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Quantitative evaluation of the cerebellum in patients with depression and healthy adults by VolBrain method

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Abstract

Objectives: Besides the well-known sensorimotor control function, the cerebellum is also associated with cognitive functions and mood via the cerebral-cerebellar circuit. This study aimed to investigate possible cerebellar morphometric changes in untreated patients with depression.

Methods: Brain magnetic resonance (MR) images of 40 adults (age: 18–50 years), including 20 untreated depression patients and 20 healthy controls were analysed prospectively. Intracranial cavity and total cerebellar volumes were measured by using VolBrain. The cerebellum segmentation was performed with CERES to obtain the total gray matter volumes and cortical thickness of the lobules.

Results: Total cerebellar volume was 141.27±13.12 cm^3 in the depressed group and 142.63±8.01 cm^3 in the control group ($p>0.05$). The difference between males and females in the depressed group was not statistically significant ($p>0.05$). Total cerebellar volume was approximately 11% of total intracranial volume in both groups. The cortical thickness of lobule V (right-total), lobule VIIIB (right), and lobule IX (right) was smaller in the depressed group, independent of sex ($p<0.05$). Lobule V, VIIIB and IX volume was smaller and Crus-I cortical thickness was increased in depressed females ($p<0.05$).

Conclusion: The cerebellar volume and cortical thickness of cerebellar lobules in patients with depression show significant differences compared to healthy subjects.

Keywords: cerebellum; depression; neuroanatomy; neuroimaging

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Introduction

Cerebellum is a major structure of the hindbrain that is located near the brainstem. It contains more neurons than the rest of the brain, but take ups only 10% of the total brain volume. This part of the central nervous system is responsible for motor learning, balance and posture, as well as coordinating of voluntary movements.[1,2] There are studies suggesting and proving that the cerebellum is also associated with cognitive functions and mood.[3–5]

The cerebellum is divided into two cerebellar hemispheres and contains a narrow midline region (vermis). It is connected to the brainstem by three peduncles. Numerous sulci and fissures of varying depth subdivide the cerebellum into 10 lobules (lobules I–X). Primary fissure and posterolateral fissure, which are deeper than other fissures, divide the lobules into 3 main subdivisions as anterior lobe (lobules I–V), posterior lobe (lobules VI–IX), and flocculonodular lobe (lobule X). Three subdi-

visions of lobule VII (crus I, crus II, VIIB) and two subdivisions of lobule VIII (VIIIA, VIIIB) have been identified in cerebellar hemispheres.[2,5] Lobules I–V, a part of lobule VI and lobule VIII are the sensorimotor cerebellum. Lobules VI, crus I, crus II, lobule VIIB and lobule IX are the cognitive cerebellum. There are also definitions of "limbic cerebellum" or "emotional cerebellum" due to the relations of the sections in the cognitive cerebellum with the limbic system.[6,7]

Depression is a mood disorder which occurs with varying severity according to the number, type, and intensity of symptoms. Nowadays, worldwide accepted guideline (Diagnostic and Statistical Manual of Mental Disorders, DSM) is used to diagnose depression and determine the severity of the disease in individuals with depressive symptoms.[8] Furthermore, neuroimaging studies have also been conducted to detect volume changes in the brain and cerebellum in cases with depression.[9,10]

Manual measurements[11] and web-based fully automatic measurements were used in the studies investigating cerebellar volume changes.[6,12,13] Moreover, it has been emphasized that the recently developed fully automated multi-atlas applications that can be accessed remotely, such as VolBrain (MRI brain volumetric system) and CERES (A cerebellar segmentation tool) have the advantage of minimizing the manual volume measurement errors.[14–16]

This study aimed to evaluate the volume and cortical thickness changes in the segmental structures of the cerebellum by volumetric methods in patients with newly diagnosed depression and in healthy adults.

Materials and Methods

Depressed and control (non-depressed) groups were determined by a psychiatrist among individuals who applied to the psychiatry clinic of Selçuk University Medical Faculty Hospital. Brain magnetic resonance (MR) images of the participants were obtained in the radiology department of the same hospital. MR images have been processed and analysed by engineers and anatomists.

Twenty patients (14 females, 6 males) with depression between the ages of 19–47 and 20 healthy adults (9 females, 11 males) between the ages of 18–50 were included in the study. The depressed and control group was composed of individuals who applied to the psychiatry clinic. Beck Depression Test was applied to the individuals during a one-on-one interview by a psychiatrist. Scoring on the Beck depression scale can range from 0 to 63. An individual with a score of less than 10 is considered as healthy, while more than 10 is considered to have depression.[17] Accordingly, the depressed group composed of patients who got more 10 points on the Beck depression test and who were diagnosed with depression according to the DSM-4 diagnostic criteria. All the patients were more than 18 years of age and did not receive any medication before the diagnosis. The control group composed of individuals who scored less than 10 points in the Beck depression test and had sociodemographic characteristics similar to the group with depression. The individuals who had previously diagnosed as depression, who had received any medication because of depression, who had familial predisposition to depression, who had previously used any addictive drug or substance, who had brain surgery due to trauma or any kind of brain pathology, and who are younger than 18 years of age are not included to the study.

MR imaging in the depressed and control groups was performed by the same technician using a 1.5 T MAGNETOM Aera (Siemens, Germany). Brain MR images were acquired with a three-dimensional, T1-weighted rapid gradient echo (MPRAGE) array of high resolution 160 sections with DICOM format followed by a standardized MR protocol.: Structural T1 axial MPRAGE were acquired by the following sequences; TE: 3.54 ms, TR: 2400 ms, Fov= 192×192 matrix, flip angle= 90° and total scan time 5 min for 160 slices. T1-weighted MR images were downloaded from scanner and processed using different software. Images were saved in NIFTI format on a personal computer on a 64-bit Dell PC running Windows 10 operating system.

VolBrain (https://VolBrain.upv.es) is an online MRI brain volumetric system intended to help researchers automatically analyse volumetric brain data from MRI data without the need for any infrastructure. This system computation an anonymized MRI intracranial cavity volume (ICC; was defined as the sum of all white matter, grey matter and cerebrospinal fluid) NIFTI format and provides volume information of some macroscopic areas such as brain hemispheres, cerebellum and brainstem. The CERES (https://VolBrain.upv.es/members.php) pipeline on the VolBrain gets an anonymized MRI brain volume in NIFTI format and produces a pdf report containing volume and thickness of cerebellar lobules. It also provides cerebellar cortical thickness for each lobule.[14–16]

The NIFTI images of all subjects (20 depressed, 20 control) was uploaded separately to the VolBrain (https://VolBrain.upv.es) by using personal e-mail.

VolBrain pdf reports containing ICC and total cerebellar volume (TCV) and CERES pdf reports containing volume and cortical thickness of cerebellar lobules (I–II, III, IV, V, VI, Crus I, Crus II, VIIB, VIIIA, VIIIB, IX, X) have been send to the same e-mail address (**Figures 1–3**).

The percentage differences (PD) of volume (cm^3) and cortical thickness (mm) data between groups and gender were determined by using the following formulas. PD were calculated based on the mean and median values.[18]

PD between case and control =
[[depressed–non-depressed]/
[(depressed+non-depressed)/2]] × 100

PD between gender =
[[male- female]/[male+female]/2]] × 100

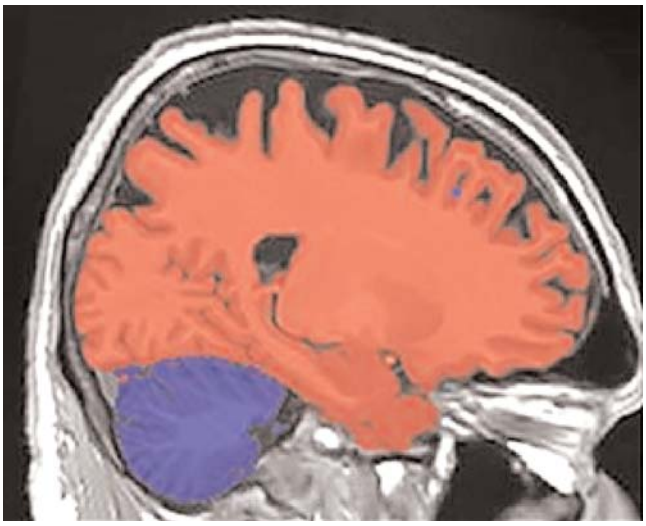

Figure 1. Demonstration of cerebellum with VolBrain.

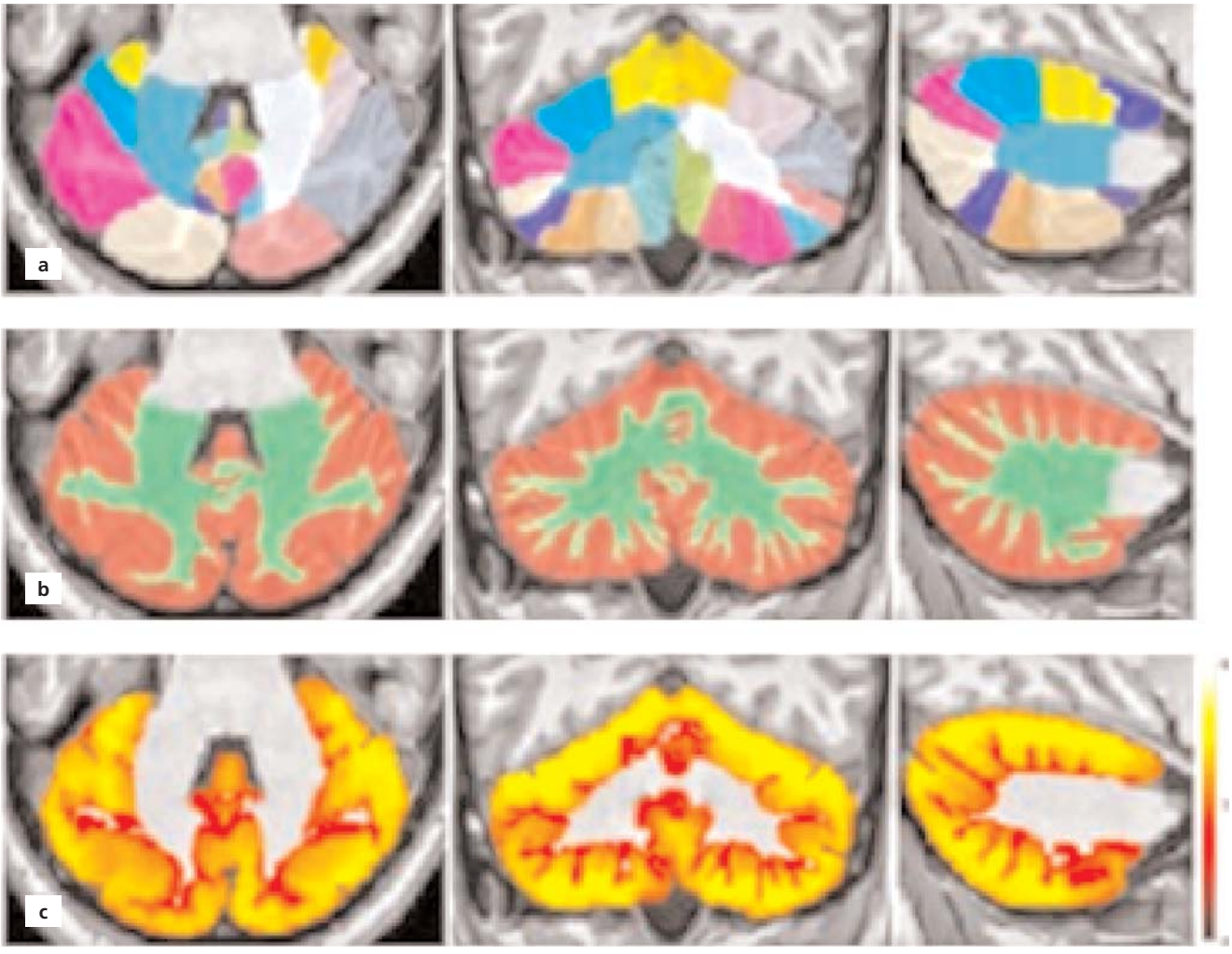

Figure 2. Segmentation of cerebellum. (**a**) lobules shown in different colours; (**b**) demonstration of white matter (**green**) and grey matter (red); (**c**) and demonstration of cerebellar cortex (**yellow**) obtained by CERES from the MR image of a 21-year-old depressed female patient.

CERES Volumetry Report version 1.0 release 03-10-2018

Patient ID	Sex	Age	Report Date
job270965	Female	21	24-Dec-2020

Image Information

Orientation	radiological
Scale factor	0.69
SNR	16.72
Total intracranial volume (cm^3)	1282.56

Volumes	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asym.(%)
Cerebellum	112.31 (8.7564) [8.0672, 10.8352]	55.61 (4.3358) [4.0362, 5.4162]	56.70 (4.4206) [4.0178, 5.4322]	-1.9363 [-4.1753, 4.2355]
Lobule I-II	0.12 (0.0092) [0.0041, 0.0322]	0.06 (0.0049) [0.0019, 0.0148]	0.06 (0.0044) [0.0017, 0.0178]	10.5263 [-53.0108, 29.3219]
Lobule III	1.48 (0.1150) [0.0837, 0.1714]	0.70 (0.0543) [0.0419, 0.0864]	0.78 (0.0607) [0.0399, 0.0869]	-11.0590 [-21.1375, 23.4735]
Lobule IV	4.88 (0.3807) [0.2338, 0.4308]	2.36 (0.1838) [0.1073, 0.2199]	2.52 (0.1968) [0.1164, 0.2210]	-6.8243 [-32.1632, 24.5926]
Lobule V	6.67 (0.5204) [0.2338, 0.4308]	3.13 (0.2442) [0.1073, 0.2199]	3.54 (0.2762) [0.1164, 0.2210]	-12.2618 [-32.1632, 24.5926]
Lobule VI	13.93 (1.0860) [1.0124, 1.6499]	7.12 (0.5551) [0.4990, 0.8340]	6.81 (0.5309) [0.4970, 0.8324]	4.4564 [-16.2985, 16.5718]
Lobule Crus I	26.58 (2.0726) [1.4952, 2.4689]	13.25 (1.0329) [0.7353, 1.2382]	13.33 (1.0397) [0.7439, 1.2468]	-0.6501 [-14.4872, 12.2639]
Lobule Crus II	14.73 (1.1485) [0.8580, 1.5444]	7.48 (0.5834) [0.4240, 0.7954]	7.25 (0.5651) [0.4163, 0.7668]	3.1910 [-16.8116, 22.0961]
Lobule VIIB	7.78 (0.6066) [0.5120, 0.8921]	3.91 (0.3046) [0.2525, 0.4619]	3.87 (0.3020) [0.2441, 0.4456]	0.8529 [-19.5159, 26.5514]
Lobule VIIIA	8.83 (0.6882) [0.6589, 1.1006]	4.27 (0.3332) [0.3174, 0.5527]	4.55 (0.3550) [0.3198, 0.5697]	-6.3273 [-26.0779, 21.2538]
Lobule VIIIB	6.68 (0.5207) [0.4201, 0.7143]	3.06 (0.2388) [0.2030, 0.3679]	3.62 (0.2819) [0.2010, 0.3625]	-16.5821 [-24.1481, 26.1173]
Lobule IX	5.42 (0.4227) [0.3649, 0.7380]	2.69 (0.2099) [0.1845, 0.3687]	2.73 (0.2128) [0.1778, 0.3719]	-1.4025 [-12.6362, 13.5494]
Lobule X	1.17 (0.0915) [0.3649, 0.7380]	0.61 (0.0474) [0.1845, 0.3687]	0.56 (0.0440) [0.1778, 0.3719]	7.4249 [-12.6362, 13.5494]

Cortical thickness	Mean (*mm/norm.*)	Right (*mm/norm.*)	Left (*mm/norm.*)	Asym.(%)
Cerebellum	4.34 (3.998) [4.062, 4.659]	4.37 (4.018) [4.038, 4.676]	4.32 (3.979) [4.059, 4.668]	0.9586 [-0.0779, 0.0845]
Lobule I-II	1.57 (1.445) [0.530, 2.445]	1.44 (1.325) [0.482, 2.394]	1.68 (1.543) [0.534, 2.499]	15.0296 [-0.4798, 0.7235]
Lobule III	3.13 (2.885) [2.237, 3.833]	3.04 (2.796) [2.155, 3.821]	3.22 (2.960) [2.234, 3.916]	5.6609 [-0.3184, 0.4281]
Lobule IV	4.73 (4.352) [3.835, 4.944]	4.62 (4.250) [3.786, 4.963]	4.83 (4.446) [3.817, 4.983]	4.4883 [-0.1607, 0.1803]
Lobule V	4.55 (4.189) [3.835, 4.944]	4.52 (4.161) [3.786, 4.963]	4.58 (4.214) [3.817, 4.983]	1.2620 [-0.1607, 0.1803]
Lobule VI	4.77 (4.394) [4.122, 4.916]	4.82 (4.433) [4.089, 4.941]	4.73 (4.353) [4.109, 4.933]	-1.8191 [-0.1152, 0.1219]
Lobule Crus I	4.26 (3.924) [3.936, 4.750]	4.32 (3.976) [3.884, 4.786]	4.21 (3.872) [3.877, 4.816]	-2.6428 [-0.1913, 0.2013]
Lobule Crus II	4.01 (3.689) [4.098, 4.847]	4.11 (3.782) [4.082, 4.882]	3.91 (3.596) [4.041, 4.877]	-5.0451 [-0.1544, 0.1340]
Lobule VIIB	4.87 (4.481) [4.124, 4.929]	4.91 (4.522) [4.113, 4.962]	4.82 (4.438) [4.084, 4.941]	-1.8618 [-0.1316, 0.1085]
Lobule VIIIA	4.69 (4.315) [4.090, 4.914]	4.56 (4.196) [4.059, 4.952]	4.81 (4.424) [4.083, 4.916]	5.2870 [-0.1098, 0.1048]
Lobule VIIIB	4.13 (3.798) [4.057, 4.956]	4.00 (3.686) [3.962, 4.983]	4.23 (3.893) [4.093, 4.983]	5.4396 [-0.1161, 0.1754]
Lobule IX	3.57 (3.285) [2.657, 4.617]	3.75 (3.456) [2.662, 4.688]	3.38 (3.113) [2.599, 4.591]	-10.4202 [-0.3061, 0.1992]
Lobule X	2.04 (1.874) [2.657, 4.617]	1.73 (1.595) [2.662, 4.688]	2.34 (2.151) [2.599, 4.591]	29.6333 [-0.3061, 0.1992]

Grey matter vol.	Total (cm^3/%)	Right (cm^3/%)	Left (cm^3/%)	Asym.(%)
Cerebellum	83.98 (6.5479) [5.9956, 8.2106]	41.36 (3.2249) [2.9995, 4.1134]	42.62 (3.3230) [2.9857, 4.1076]	-2.9960 [-4.2532, 4.7521]
Lobule I-II	0.05 (0.0041) [0.0023, 0.0163]	0.02 (0.0019) [0.0009, 0.0076]	0.03 (0.0022) [0.0011, 0.0089]	-18.7883 [-97.3721, 52.2983]
Lobule III	1.05 (0.0819) [0.0442, 0.1055]	0.49 (0.0385) [0.0215, 0.0517]	0.56 (0.0434) [0.0213, 0.0551]	-17.5126 [-45.8571, 36.2282]
Lobule IV	4.22 (0.3288) [0.1958, 0.3617]	2.01 (0.1566) [0.0910, 0.1832]	2.21 (0.1722) [0.0957, 0.1877]	-13.7058 [-49.5257, 39.5528]
Lobule V	5.62 (0.4379) [0.1958, 0.3617]	2.65 (0.2068) [0.0910, 0.1832]	2.96 (0.2311) [0.0957, 0.1877]	-16.0230 [-49.5257, 39.5528]
Lobule VI	12.34 (0.9621) [0.8756, 1.4540]	6.28 (0.4898) [0.4290, 0.7329]	6.06 (0.4723) [0.4323, 0.7354]	5.2678 [-26.1337, 24.0047]
Lobule Crus I	22.62 (1.7633) [1.2212, 2.0699]	11.25 (0.8770) [0.5995, 1.0411]	11.37 (0.8863) [0.6053, 1.0452]	-1.5211 [-24.1779, 21.6198]
Lobule Crus II	12.64 (0.9858) [0.7376, 1.3581]	6.38 (0.4972) [0.3624, 0.6956]	6.27 (0.4887) [0.3592, 0.6785]	2.4992 [-27.7484, 33.1191]
Lobule VIIB	6.93 (0.5401) [0.4495, 0.7921]	3.51 (0.2734) [0.2249, 0.4148]	3.42 (0.2667) [0.2110, 0.3909]	3.5514 [-25.7706, 42.8813]
Lobule VIIIA	7.60 (0.5922) [0.5745, 0.9634]	3.63 (0.2827) [0.2776, 0.4855]	3.97 (0.3095) [0.2777, 0.4970]	-13.0608 [-38.3874, 33.3614]
Lobule VIIIB	5.43 (0.4231) [0.3495, 0.6123]	2.46 (0.1919) [0.1683, 0.3148]	2.97 (0.2313) [0.1667, 0.3121]	-26.9401 [-37.9655, 40.5584]
Lobule IX	4.14 (0.3225) [0.2635, 0.5786]	2.05 (0.1595) [0.1353, 0.2928]	2.09 (0.1630) [0.1252, 0.2888]	-3.0945 [-19.7674, 30.5306]
Lobule X	1.06 (0.0823) [0.2635, 0.5786]	0.53 (0.0414) [0.1353, 0.2928]	0.52 (0.0409) [0.1252, 0.2888]	1.7053 [-19.7674, 30.5306]

Figure 3. CERES Volumetry Report showing the cerebellar volume and cortical thickness of a 21-year-old depressed female patient.

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows (Version 21, Chicago, IL, USA). Histogram graphs and Kolmogorov-Smirnov test were used to determine the compliance of the variables to the normal distribution. It was determined that the data of the participants were distributed normally for the depressed and non-depressed groups, regardless of sex, but not distributed normally in the groups according to sex. Normally and non-normally distributed continuous variables were compared with Student's t-test and Mann-Whitney U test, respectively. For all analyses; $p<0.05$ was considered as statistically significant.

Results

The mean age of the participants was 29.85±11.50 (range: 19–47 years) in the depressed group and 29.90±8.55 (range: 18–50 years) in the non-depressed group. There was no statistically significant difference ($p>0.05$) between the mean ages of the two groups.

The mean ICC volume was 1423.19±131.27 cm^3 in the depressed group and 1426.8±91.44 cm^3 in the control group. The mean total cerebellar volume was 141.27±13.12 cm^3 in the depressed group and 142.63±8.01 cm^3 in the control group. Total cerebellar volume was approximately 11% of ICC volume in both depressed and control groups. The differences between ICC volume and total cerebellar volumes in the depressed and control groups were not statistically significant ($p>0.05$). In the depressed group, the ICC volume was statistically significantly bigger in males ($p<0.005$) (**Table 1**). PD between males and females was calculated as 13.68 for ICC volume and 8.30 for total cerebellar volume in the depressed group. It was remarkable that the PD determined by sex was lower in the non-depressed group.

In the second part of the volumetric analysis, the total and grey matter volumes and cortical thicknesses of the 10 lobules of the cerebellum were calculated with CERES (**Tables 2** and **3**). Comparison of lobular volume and cortical thickness between the depressed and control groups showed statistically significant differences in only a few lobular cortical thickness. The cortical thickness of lobule V (total and right), lobule VIIIB (right), and lobule IX (right) were statistically significantly smaller in the depressed group ($p<0.05$) (**Table 2**). Comparison between the groups according to sex showed no difference between the depressed and the control groups, while statistically significant differences were found regarding the volume and cortical thickness of cerebellar lobules between the males and females in

Table 1

Comparison of intracranial cavity volume (cm^3) and total cerebellar volume (cm^3) in depressed and control groups according to sex.

	Depressed						Control					
	Male (n=6)		Female (n=14)				Male (n=11)		Female (n=9)			
	Median	Perc.	Median	Perc.	p-value	PD	Median	Perc.	Median	Perc.	p-value	PD
ICCV*	1571.83	1495.99[a] 1631.83[b]	1370.53	1281.02[a] 1473.90[b]	.001†	13.68	1415.19	1376.05[a] 1513.26[b]	1395.94	1324.12[a] 1473.99[b]	.261	1.36
TCV*	150.52	133.86[a] 158.77[b]	138.52	132.31[a] 147.69[b]	.312	8.30	143.70	137.82[a] 148.11[b]	141.26	135.74[a] 144.61[b]	.289	1.71

*Mann-Whitney U test; †p<0.05; [a]25th percentile; [b]75th percentile. **ICCV:** intracranial cavity volume; **PD:** percentage difference according to sex; **Perc:** percentiles **TCV:** total cerebellar volume.

the depressed group. The volume and cortical thickness of lobule V (right, left, total), and the volume of lobule VIIIB (right) and lobule IX (left, total) were significantly smaller in depressed women (p<0.05). Crus I (right, left, total) cortical thickness of depressed women was significantly higher than depressed males (p<0.05). While the percentage of male-female PD in the volumes with statistically significant differences was between 17.94 and 30.39, the PD for cortical thickness was between 3.12 and 8.65 (**Table 3**).

Discussion

The location of the cerebellum in the posterior cranial fossa, makes it difficult to define its size, position and lobes. The morphology of the cerebellum and its morphological changes in pathological processes have been subject of previous studies. Cerebellar volumes of patients suffering from nervous system diseases (major depression, dementia, bipolar disorder, schizophrenia, monocular blindness, chronic tinnitus) were measured with different methods.[6,11,19–22] In some of these studies, VolBrain and similar volumetric methods were used, which provide automatic and accurate segmentation of the cerebellum on standard resolution T1-weighted brain MR images.[6,20–23]

The neurobiological processes that lead to depression have not been fully understood in extensive preclinical and clinical studies. Current studies have related depression with a reduction in the number and/or size of glia and neurons in different brain regions.[23,24] The role of the cerebellum in regulating emotions has been given more serious consideration over the past three decades. Complex connections between cortical areas such as the cerebellum and prefrontal cortex have been demonstrated with functional neuroimaging methods,[25] also studies based on clinical experience have been conducted in children and adults with cerebellar lesions who have emotional disorders.[26] There are also some volumetric studies on images of people diagnosed with affective disorders. Decrease in cerebellar volume has been reported in studies in cases of major depression and it is considered to be associated with the severity of the disease.[1,6,11,12] The present study aims to determine the differences in cerebellar volume and cortical thicknesses in patients who are diagnosed with depression regardless of its severity. The patients included in our study have not

Table 2

Statistically significant differences in the cerebellar volumes and cortical thickness between the depressed and control groups and the percentage differences.

	Depressed (n=20) Mean±SD	Control (n=20) Mean±SD	p-value	PD
Lobule V total cortical thickness (mm)*	4.67±1.38	4.75±0.10	.036†	1.69
Lobule V right cortical thickness (mm)*	4.56±1.15	4.68±0.15	.024†	2.59
Lobul VIIIB right cortical thickness (mm)*	4.26±0.23	4.42±0.25	.046†	3.68
Lobul IX right cortical thickness (mm)*	3.64±0.34	3.84±0.24	.042†	5.34

*Independent t-test; †p<0.05. **PD:** percentage difference (depressed vs control).

Table 3

The cerebellar volume and the percentage differences with statistically significant differences between males and females in the depressed group.

		Depressed					
		Male (n=6)		Female (n=14)			
		Median	Percentiles	Median	Percentiles	p-value	PD
Lobule V (right)*	TV	5.16	4.30† 6.05‡	3.95	3.51† 4.59‡	.033§	26.56
	GMV	4.34	3.63† 5.07‡	3.38	2.84† 3.76‡	.020§	24.87
	CT	4.72	4.61† 4.75‡	4.48	4.43† 4.59‡	.006§	5.21
Lobule V (left)*	TV	4.98	4.25† 5.70‡	4.16	3.51† 4.25‡	.003§	17.94
	GMV	4.40	3.73† 5.03‡	3.59	2.95† 3.74‡	.002§	20.27
	CT	4.88	4.84† 4.92‡	4.73	4.57† 7.87‡	.020§	3.12
Lobule V (total)*	TV	10.14	8.55† 11.75‡	8.09	7.09† 8.80‡	.015§	22.49
	GMV	8.75	7.37† 10.10‡	7.03	6.01† 7.42‡	.050§	21.79
	CT	4.79	4.77† 7.80‡	4.59	4.54† 4.76‡	.005§	4.26
Crus I (right)*	CT	4.04	3.88† 4.11‡	4.35	4.09† 4.44‡	.006§	7.38
Crus I (left)*	CT	3.87	3.74† 4.07‡	4.22	4.15† 4.30‡	.015§	8.65
Crus I (total)	CT	3.93	3.88† 4.08‡	4.28	4.16† 4.38‡	.006§	8.52
Lobule VIIIB (right)*	TV	4.54	4.17† 4.77‡	3.54	3.21† 4.28‡	.026§	24.75
	GMV	3.79	3.41† 4.03‡	2.79	2.52† 3.61‡	.015§	30.39
Lobule IX (Left)*	TV	3.94	3.59† 4.54‡	2.99	2.72† 3.72‡	.033§	27.41
	GMV	3.04	2.77† 3.54‡	2.35	2.09† 2.93‡	.033§	25.60
Lobule IX (Total)*	TV	7.90	7.20† 8.98‡	5.98	4.47† 7.61‡	.033§	27.66
	GMV	6.35	5.98† 7.57‡	5.14	4.51† 6.48‡	.041§	21.06

*Mann-Whitney U test; †25th percentile; ‡75th percentile; §p<0.05). **CT:** cortical thickness (mm); **GMV:** Gray matter volume (cm^3); **PD:** percentage difference (males vs females); **TV:** total volume (cm^3).

been treated with any medication, and the healthy volunteers had the same sociodemographic characteristics.

The studies in which the total cerebellar volume was calculated by manual methods on MR images of healthy individuals revealed significant differences according to sex (females, 115±11.29–134.6±6.8 cm^3; males, 126.01±10.38–152.2±10.5 cm^3).[27–29] In our automatic segmentation study, the total cerebellar volume in the healthy control group was 141.26 (135.74–144.61 cm^3) in women and 143.70 (137.82–148.11 cm^3) in men, but there was no statistically significant difference. The total cerebellar volume was approximately 11% of the ICC volume in both groups, consistent with the literature. Previous MRI studies showed shrinkage in some parts of the cerebellum with increasing age.[29,30] We did not include individuals elder than 50 years of age and we did not investigate the effect of age. However, it is understood from the literature that there is no consensus on the effects of age and sex on the size of the cerebellum.

Yılmaz et al.[16] calculated the total cerebellar volume as 152.12±20.40 cm^3 (95.45–183.72 cm^3) in 18 healthy males (22–30 years) using the VolBrain method. In our study, the total volume of the cerebellum was calculated as 150.52 cm^3 (133.86–158.77 cm^3) in depressed males and 143.40 cm^3 (137.82–148.11 cm^3) in non-depressed males with the same method. There was no statistically significant difference between the volumes of males in both groups. Differences in male total cerebellar volumes calculated by the same method may be due to number of the participants and individual differences.

Escalona et al.[11] investigated the effects of age, diagnosis of depression and sex on the total cerebellar volume in MR images using a manual method (Cavalier method). They emphasized that while age was not effective on cerebellar volume, depression and sex had a significant effect. The cerebellar volumes calculated by Escalona et al.[11] were 129.3±18 ml (females: 122.6±14 ml; males: 140.7±20 ml; PD: 13.74) in depressed patients and 143±5 ml (females: 136.6±12 ml; males: 149.8±15 ml; PD: 9.21) in the control group. Although they found the cerebellar volume smaller in the depressive group, they could not precisely mention whether the findings were present before the onset of symptoms, during the course, or secondary to the treatment received, since there were no pre-diagnosis MR images. In our study, the cerebellar volumes in the control group were similar to the results of Escolana et al.,[11] but not in the depressed group. While the difference between female and male cerebellar volumes was statistically significant ($p<0.005$) in the study of Escalona et al.,[11] no statistically significant difference was found in our study. Differences in cerebellar volume between the two studies may be due to differences in the severity of depression (major depression/newly diagnosed and untreated depression), measurement techniques (manual volume measurement/automatic multiple atlas applications), sample size and exclusion criteria (familial predisposition).

Previous studies used different automatic software to evaluate the relationship of depression with cerebellar (total, lobular) volumes and/or cortical thickness.[6,12,13,31] Depping et al.[6,12] analyzed post-treatment (medication and electroconvulsion) MR images of major depression cases with a voxel-based analysis method (Spatially Unbiased Infratentorial Toolbox -SUIT) and reported an increase in grey matter in some regions (IX, right VIIIa, left VIIb) compared to the control group. Bogoian et al.[13] showed a correlation between the volumes of lobule VI and lobule VIII and symptoms in 38 healthy adults (age: 51–80 years) who had depressive symptoms but were not diagnosed with depression. In these studies, data were not compared according to age and sex. Kim et al.[31] investigated the relationship between post-stroke depression and lesion site using MRIcron software on T1-weighted MR images in patients with isolated cerebellar stroke. They concluded that left cerebellum (especially crus II) damage was associated with the occurrence and severity of depression.

In our study, only the cortical thickness of lobule V, lobule VIIIB and lobule IX was significantly smaller in the depressed group regardless of sex. In addition, there were statistically significant differences between males and females in the volumes of lobule V, lobule VIIIB, and lobule IX in the depressed group, and in the cortical thickness of lobule V and crus I. In the depressed group, the percent difference between men and women was large regarding the volume (17.94–30.39) and small regarding the cortical thickness (3.12–8.65). In the control group, there was no significant difference between males and females in any of the 10 cerebellar lobules data.

The present study has some limitations. Firstly, the number of the samples were small and secondly; depression severity was not categorized and analysis by severity was not performed. Thirdly, the gender distribution in the groups was not equal. On the other hand, the unique aspect of the study is the inclusion of patients who had not received any medication before. Thus, the effect of the treatment can be the eliminated.

Conclusion

We evaluated the volume and cortical thickness of the anatomical subdivisions of the cerebellum in patients with depression at the time of diagnosis. The results of the study suggest that the changes in cortical thickness (particularly lobule V, VIII and IX) might be the initial morphological changes, which can be detected at the onset of depression. We believe that the determination of cerebellar volume and cortical thickness in people with depressive symptoms might help the early diagnosis and proper management of the patients with depression. Further studies with larger samples should be carried out to address these suggestions.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

OG: project development, data collection; GO: project development, data collection, data analysis, manuscript writing; SO: project development, data collection; YP: data collection; DAS: project development, data processing, statistical analysis, manuscript writing; İİU: project development, statistical evaluation, manuscript editing.

Ethics Approval

All procedures were approved by the Ethical Committee of Selçuk University (approval number 2016/310).

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